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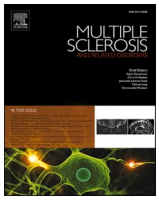

Original article

Management of patients with active relapsing-remitting or secondary progressive multiple sclerosis: A French real-world study based on claims data linked to a phase IV study

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ABSTRACT

Background: PRO-MSactive is a French phase-IV study evaluating ocrelizumab efficacy in active relapsing-remitting or secondary progressive multiple sclerosis (RRMS or SPMS). By linking clinical data to the national claims database (SNDS), the objective of this study was to obtain an overview of RRMS and SPMS burden.
Methods: All RRMS and SPMS patients included in the PRO-MSactive study between July 2018 and July 2019 and followed for 48 weeks were linked to MS patients from SNDS. Healthcare Resource Utilization and costs were described in RRMS patients, in the two years prior to ocrelizumab initiation, by 12 months period (n-1 and n-2), according to EDSS score (< 4 versus ≥ 4).
Results: 291/371 patients (78.7 %) were included: 257 RRMS and 34 SPMS patients. Different costs according to disability status (year n-2: 9,103€ versus 16,441€; year n-1: 9,813€ versus 19,999€, for patients with score EDSS <4 versus ≥ 4, respectively) and relapse activity (+1,358€ between year n-2 and n-1) were observed.
Conclusion: This study is the first to combine clinical data from a phase-IV study with a claims database allowing to distinguish costs according to disease type. We objectified a greater economic burden in RRMS patients with higher levels of disability and showed an increase in costs associated with relapse activity in the 2 years before enrolling in the phase IV study.

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and degenerative disease of the central nervous system (CNS), affecting approximately 2.9 million patients worldwide and about 135,000 in France in 2021 (MS international federation, 2020, Pierret et al., 2024). MS is clinically subcategorized into three phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and progression of disability. These include relapsing remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS), where the combination of RRMS and SPMS represent relapsing-onset MS disease (relapsing multiple sclerosis [RMS]).

The burden of MS is high. A study conducted in 2013 showed that, as compared to 2004, cost of medications increased by 25 %, whereas costs of hospitalizations and sick leaves decreased by 23 % and 16 %, respectively (Lefeuvre et al., 2016). More recent studies have also described the economic burden of MS (Vandhuick et al., 2021, Bruno et al., 2019). Indeed, as our understanding of the disease has evolved, significant progress has been made in its treatment over the past thirty years (Leblanc et al., 2022). The current therapeutic approach in MS involves treatment of relapses and disease modifying therapies (DMTs).

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DMTs are the mainstay for the pharmacological treatment of MS. These therapies aim to decrease the annualized relapse rate, as well as to slow disease progression and disability accumulation (Giovannoni et al., 2020). The marketed DMTs have a wide range of mechanisms of action and can be immunomodulatory, or immunosuppressive drugs.

Among immunosuppressive drugs, ocrelizumab, a humanized CD20 monoclonal antibody, demonstrated a favorable benefit risk ratio in RMS and PPMS patients (Hauser et al., 2021), leading the European Commission to grant marketing authorization on January 08, 2018 (EMA 2022). In France, ocrelizumab has been reimbursed since February 28, 2019, only for the treatment of RMS patients with active disease defined by clinical or imaging features.

The PRO-MSACTIVE study was designed to provide additional data in France on ocrelizumab efficacy, safety and Patient Reported Outcomes (PRO) measures in a pragmatic setting. This study is an interventional national, multicenter, open-label, single-arm, phase IV study conducted in 422 patients with active RRMS or active SPMS (Manchon et al., 2022).

The aim of the present study was to describe treatment patterns, Healthcare Resource Utilization (HRU) and costs of management of patients with active RMS before initiating ocrelizumab. Linking routine healthcare claims data from the national health data system (*Système National des Données de Santé*, [SNDS]) with efficacy and safety data, collected as part of an interventional study, constitutes an innovative approach useful for answering different research questions.

2. Materials and methods

2.1. Data sources and linkage

This retrospective, population-based cohort study was based on two complementary data sources. On the one hand, claims data from the SNDS, which covers >98 % of the French population and contains anonymous individual information on sociodemographic characteristics, all non-hospital reimbursed healthcare expenditures, and all hospital discharge summaries (ICD10-code-based) (Tuppin et al., 2017). However, the SNDS does not provide direct information on disability status (no Expanded Disability Status Scale [EDSS] score) or disease activity, such as relapses or lesions due to unavailability of imaging results. Except for specific costly medications, no information is available on drugs dispensed during a hospital stay.

On the other hand, clinical data from the PRO-MSACTIVE study were also used. This phase IV study was conducted in 376 patients with RRMS and 46 with SPMS. These patients received an injection of ocrelizumab at day 1 (initiation), week 2 (W2), week 24 (W24), and week 48 (W48), which was the only injection not supported as part of the Phase IV study and available in the SNDS database. A follow-up visit was planned at week 72 (W72), during which an injection may have been performed. Patients were included from July 1, 2018 to July 31, 2019. The main data collected were medical history and demographic data, disease activity data (potential relapses, brain Magnetic Resonance Imaging [MRI]), disability status (EDSS score), PROs, concomitant treatment.

A deterministic linkage was performed to link SNDS and PRO-MSACTIVE data. The main variables used were year of birth, gender, date of ocrelizumab infusion at W48, hospital reference number, years and name of previous MS treatment, date of the last MRI before ocrelizumab initiation. When these variables were insufficiently discriminating and data were available, the date of W2, W24 or W72 were used as additional linkage variables. The first step was to create couples between patients of both data sources on all main variables. Then, several successive rounds of linkage were carried out by removing main variables according to data quality - except sex, age and hospital reference number - using additional linkage variables, adding a 3-day margin of error around the date at W48 or looking for matches with other ocrelizumab dispensing in the SNDS than those expected. Lastly, only patients for whom the ocrelizumab injection in the SNDS did not correspond to an initiation, i.e. no ocrelizumab injection registered during the following 30 days, were considered to be correctly linked.

2.2. Population

All patients with MS between January 1, 2013 and December 31, 2020 were extracted from the SNDS using the ICD-10 code G35 from hospitalizations discharges and Long-Term Disease status (LTD), except those with a reimbursement of ocrelizumab under Temporary Use Authorization (TUA) /post-TUA, i.e. before February 28, 2019. All patients included in the ML40359 PRO-MSACTIVE study, with ocrelizumab infusion at W48 and who received an individual information note, were likely to be linked to the SNDS database. Patients with a period of two years without any reimbursed care in the SNDS from the date of MS diagnosis, or during the 5 years prior to ocrelizumab initiation if the diagnosis date was >5 years before, were excluded.

2.3. Study periods

The inclusion period, corresponding to that of the ML40359 PRO-MSACTIVE study, ran from July 1, 2018 to July 31, 2019. The index date was defined as the date of initiation of ocrelizumab. A pre-study period of 5 years prior to index date was used. Patients were followed-up from index date to the earlier of: last patient's health record, i.e. last care before a period of 12 months without reimbursed care; end of study period (i.e. December 31, 2020); or death.

2.4. Variables

To study the pattern of ocrelizumab use, first-line therapy use was defined as the absence of treatment between the date of diagnosis and the inclusion in ML40359 PRO-MSACTIVE study, or during the 5 previous years if the diagnosis date was >5 years ago. MS-specific DMTs were classified according to their place in the therapeutic strategy, i.e. as moderate efficacy DMT (Interferons, Dimethyl fumarate, Glatiramer acetate, Teriflunomide) or high efficacy DMT (Fingolimod, Natalizumab). cladribine (Cladribine) and ponesimod were not yet marketed at that time and alemtuzumab and mitoxantrone, being only dispensed at hospital, were not available in the SNDS database. As rituximab has no marketing authorization in MS, it was not considered for the definition of treatment regimens, but was taken into account to define naive/non-naive status. The treatment sequence was defined as the succession of treatment lines and treatment-free intervals, corresponding to periods of at least 3 months without any MS-specific DMT. A treatment line was defined as completed when a dispensing of a different MS-specific DMT, or a period of at least 3 months without DMT dispensing after the end of coverage period of the last dispensing, was recorded.

The following HRU items were described: medications, medical devices, medical/paramedical visit, medical procedures, lab tests, hospitalization for MS, sick leaves, disability pensions, and medical transports. Hospitalizations were described both overall and separately for day (which include those for natalizumab injections) versus full hospitalization.

2.5. Statistical analyses

Treatment patterns were described from MS diagnosis, or over the five years prior to if the diagnosis date was >5 years before ocrelizumab initiation, in RRMS and SPMS patients. HRU were analyzed only in RRMS patients because the number of SPMS patients was deemed too small. Each health expenditure item was described according to the EDSS score and over two periods: [−24; −12 [months (year n-2) and [−12; 0 [months (year n-1) prior to ocrelizumab initiation. For each HRU, the percentage of users (i.e. patients with at least one record) and the mean number of cares per patient in users were reported for each period. The monthly cost per patient from health insurance perspective

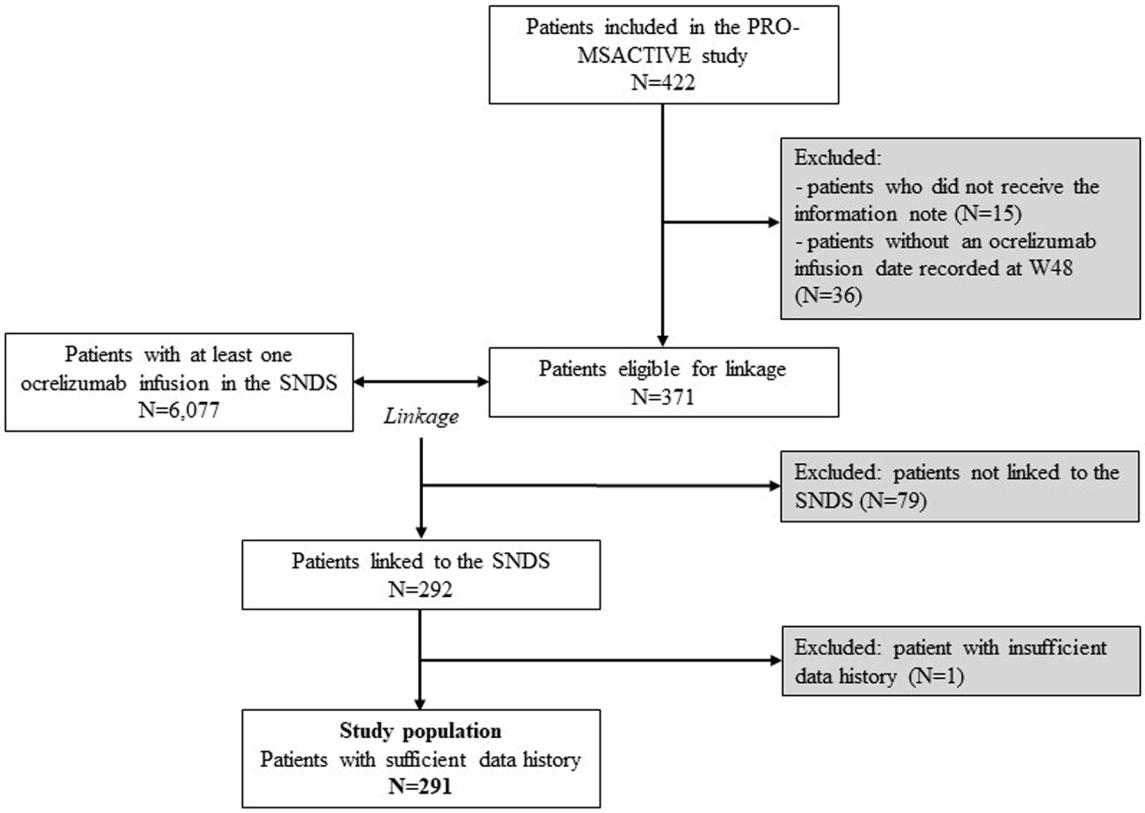

Fig. 1. Study population flow chart.

Table 1
Rounds of linkage between the ML40359 PRO-MSACTIVE and SNDS data.

Round	Basic variables*	Injection date - W48			Injection date - W72			Injection date - W2 or W24	MRI	Years of treatment	Linkage patients	
		1st disp.	1st disp. +/-3 days	≠ 1st disp.	1st disp.	2nd disp.	≠ 1st disp.				Number of pairs 1:1	Cumulative patients, N (%)
1	■	■							■	■	56	56 (15.1%)
2	■	■				■			▒	▒	104	160 (43.1%)
3	■	■				■					29	189 (50.9%)
4	■	■							▒	▒	51	240 (64.7%)
5	■	■									25	265 (71.4%)
6	■		■			▒			▒	▒	4	269 (72.5%)
7	■			■			▒	■	▒	▒	10	279 (75.2%)
8	■				■				▒	▒	13	292 (78.7%)
9	■						■	■	▒	▒	0	292 (78.7%)

*Agreement between clinical database and SNDS on sex, year of birth and hospital reference number

1st disp.: Agreement between the W48/W72 date (clinical study) and the 1st dispensing of Ocrelizumab in the SNDS

2nd disp.: Agreement between the W72 date (clinical study) and the 2nd dispensing of Ocrelizumab in the SNDS

≠ 1st disp.: Agreement between the W48/W72 date (clinical study) and a dispensing of Ocrelizumab in the SNDS, other than the first

W2/W24: Agreement between the W2 date and/or the W24 date (clinical study) and one of the Ocrelizumab dispensing in the SNDS database, to the day

MRI: Agreement between the date of the last MRI before the initiation of Ocrelizumab in the clinical database and an MRI date from the SNDS

Years of treatments: Agreement with the years of beginning and end of all treatments found in both databases (except Ocrelizumab). Variable applicable only to subjects with at least one treatment (missing data for subjects with no treatment in the SNDS database and in the clinical database)

■ Agreement required

▒ Optional variable: at least one agreement required

was computed overall and for each HRU item. HRU (percentage of users) and costs were compared according the EDSS score (<4 vs ≥4) using a chi-squared test (or Fisher's exact test when test validity conditions were not met) and Wilcoxon test, respectively. McNemar test and Wilcoxon Signed Rank Test were used for comparing HRU and costs of year n-2 and n-1, respectively. All statistical analyses were performed using SAS (SAS Institute, North Carolina, US), version 9.4.

Table 2
Characteristics of patients with RRMS and SPMS.

	RRMS (N = 257)	SPMS (N = 34)
Gender, n (%)		
Male	66 (25.7 %)	13 (38.2 %)
Female	191 (74.3 %)	21 (61.8 %)
Age at index date (in years)		
Mean (SD)	38.5 (10.0)	49.6 (7.5)
Age at index date (in years), n (%)		
< 20	6 (2.3 %)	0 (0 %)
20–39	138 (53.7 %)	2 (5.9 %)
40–59	108 (42.0 %)	28 (82.4 %)
≥ 60	5 (1.9 %)	4 (11.8 %)
Free access to care status during the year before index date, n (%)	23 (8.9 %)	1 (2.9 %)
Patients with LTD status during the year before index date, n (%)	231 (89.9 %)	30 (88.2 %)
Time since the start of the LTD status and index date (in years)		
Median (Q1 - Q3)	3.7 (0.6 - 8.8)	15.6 (8.9 - 21.0)
Time since MS diagnosis (in years)		
N (%)	255 (99.2 %)	32 (94.1 %)
Median (Q1 - Q3)	5.0 (1.6 - 9.6)	16.5 (11.4 - 24.4)
Lesions, n(%)		
0	0 (0 %)	0 (0 %)
<9	24 (9.3 %)	3 (8.8 %)
≥9	221 (86.0 %)	28 (82.4 %)
Confluent Lesions	9 (3.5 %)	3 (8.8 %)
Unknown	2 (0.8 %)	0 (0 %)
Missing values	1 (0.4 %)	0 (0 %)
Number of relapses over the past year		
N (%)	257 (100.0 %)	34 (100.0 %)
Mean (SD)	1.2 (0.8)	0.8 (0.7)
Score of last EDSS		
Missing values	37 (14.4 %)	5 (14.7 %)
<4	174 (67.7 %)	3 (8.8 %)
≥4	46 (17.9 %)	26 (76.5 %)

3. Results

3.1. Linkage

Among the 422 patients in the PRO-MSACTIVE study, of whom 376 (89.1 %) with RRMS and 46 (10.9 %) with SPMS, 371 (87.9 %) were likely to be linked to the 6077 patients with an ocrelizumab infusion in the SNDS (Fig. 1). At the first round of linkage, 56 patients (15.1 %) matched a single person in the SNDS (and conversely) on all the main linkage variables, and 265 (71.4 %) after removing MRI and previous treatment variables (Table 1). After using a 3-day margin error around the ocrelizumab infusion date at W48 and searching for a match with other ocrelizumab infusion dates in the SNDS than those expected, 27 additional patients matched a single person in the SNDS (and conversely), for a total of 292 linked patients (78.7 %). For all these 292 patients, the ocrelizumab injection in the SNDS did not correspond to an initiation. One patient had insufficient data history and was excluded, leading to a study population of 291 patients, among whom 257 (88.3 %) RRMS patients and 34 (11.7 %) SPMS patients.

3.2. Patients' description

RRMS and SPMS patients were mostly females (Table 2). About half of RRMS patients were aged between 20 and 39 years whereas >80 % of SPMS patients were aged between 40 and 59 years. At ocrelizumab initiation, RRMS and SPMS patients had been diagnosed for a median of 5.0 years and 16.5 years, respectively. More than two-thirds of RRMS patients had an EDSS score <4, whereas more than three-quarters of SPMS patients had an EDSS score ≥4. Characteristics of the 115 patients unlinked to the SNDS, including 105 (91.3 %) RRMS and 10 (8.7 %) SPMS patients, were quite similar to those of the linked patients (Supplementary Table A1).

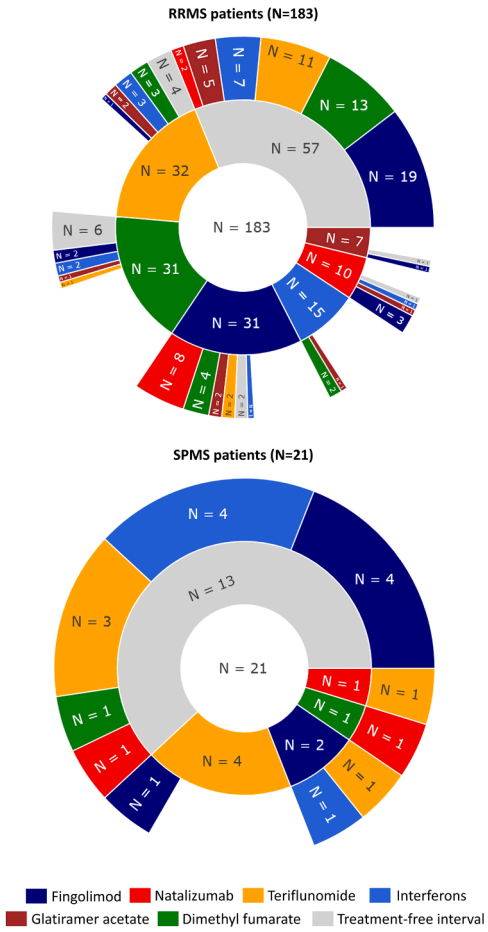

Fig. 2. Sunbursts of treatments received before ocrelizumab initiation, for RRMS and SPMS patients.

3.3. Treatment patterns

3.3.1. Patients with RRMS

Most of RRMS patients were non-naïve (71.2 %), among whom two-thirds received a moderate efficacy DMT prior to ocrelizumab initiation (Fig. 2) The median time between the last treatment received and ocrelizumab initiation was 1.8 months. Among non-naïve patients, 31.1 % had a treatment-free interval before the initiation of ocrelizumab, averaging 8.4 (±6.6) months.

3.3.2. Patients with SPMS

Most of SPMS patients were non-naïve (61.8 %), among whom 61.9 % had a treatment-free interval before the initiation of ocrelizumab, averaging 24.0 (±17.2) months. The median time between the last treatment received and ocrelizumab initiation was 4.7 months.

3.4. Healthcare resource utilization in patients with RRMS

Fingolimod and Natalizumab were more often used in patients with EDSS score ≥ 4 than those with score <4 over year n-1 (32.6 % and 15.2

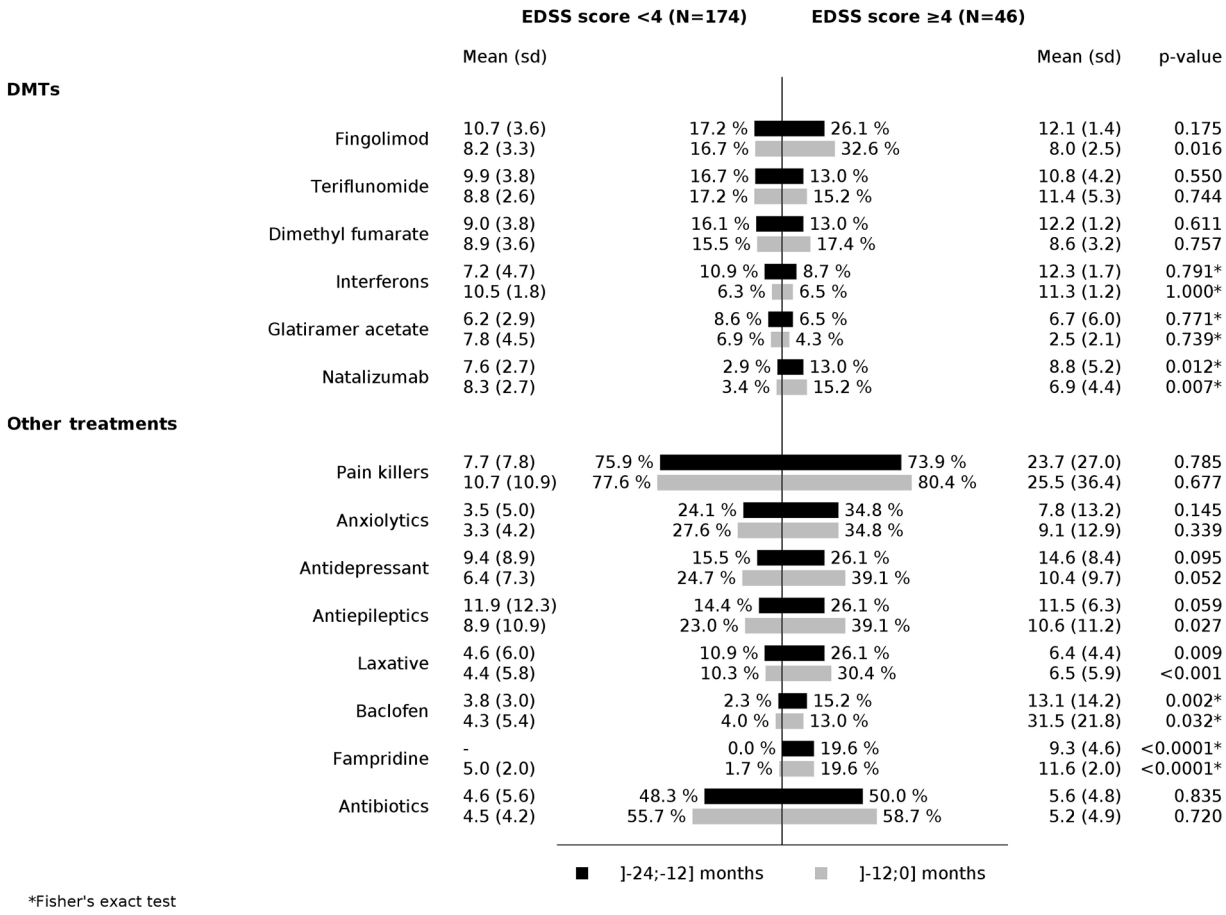

Fig. 3. MS-SPECIFIC DMTs and other treatments received by RRMS patients according to the EDSS score, over year n-2 and n-1: percentage of patients with at least one care and mean number of cares per patient.

% versus 16.7 % and 3.4 %, $p = 0.016$ and 0.007, respectively) (Fig. 3). The use of walking assistance devices and wheelchairs was higher in patients with EDSS score ≥4 over year n-1 (23.9 % and 13.0 % versus 11.5 % and 0.6 %, $p = 0.031$ and $p < 0.001$, respectively). The proportion of overall RRMS patients hospitalized at least once increased between year n-2 and n-1 (from 26.5 % (N = 68/257) to 65.4 % (N = 168/257), $p < 0.001$) and was higher in those with EDSS score ≥4 in year n-2 (43.5 % (N = 20/46) vs. 23.6 % (N = 41/174), $p = 0.007$) (Fig. 4).

3.5. Costs of care

The annual mean cost for RRMS patients increased by +1358€ [95 % CI: 360; 2357] between year n-2 and n-1, i.e. from 10,318€ [95 % CI: 9034; 11,602] to 11,676€ [95 % CI: 10,545; 12,807] ($p = 0.04$; Supplementary Fig. A1), mainly driven by MS-specific DMTs (71 % and 54 %, respectively) and hospitalizations costs (8 % and 19 %, respectively; Supplementary Fig. A2). Higher costs were observed for patients with EDSS score ≥4, over the year n-2 (16,441€ versus 9103€, $p < 0.001$) and year n-1 (19,999€ versus 9813€, $p < 0.001$) (Fig. 5). There was an increase in hospitalization costs from year n-2 to year n-1, for both patients with EDSS score <4 and ≥4 ($p < 0.001$ and $p = 0.01$, respectively) (Fig. 6). For both patients with EDSS score <4 and ≥4, the cost was mainly driven by MS treatment in years n-2 and n-1, but hospitalization costs were higher in patients with EDSS score ≥4 in year n-2 (2312€ versus 470€, $p < 0.001$) and year n-1 (5290€ versus 1343€, $p = 0.002$).

The annual mean cost for SPMS patients was 18,139€ [95 % CI: 12,481; 23,796] over the year n-2 and 16,859€ [95 % CI: 11,976; 21,743] over the year n-1 (Supplementary Fig. A3).

4. Discussion

4.1. Main findings

This study is the first to provide data from the linkage of phase IV study data with French claims data, suggesting non negligible differences in costs according to disability status (year n-2: 16,441€ versus 9103€; year n-1: 19,999€ versus 9813€, for patients with score EDSS <4 versus ≥4, respectively) and relapse activity (+1358€ between year n-2 and n-1, mainly driven by an increase in hospitalizations costs).

4.2. External validity

Several studies have already described the costs of MS in France, but for periods prior to ours. The study of Lefeuvre et al., also performed in the SNDS, estimated a cost of 14,735€/patient/year in 2013 (including direct and indirect costs) (Lefeuvre et al., 2016). Another study, which to our knowledge is the only other study to link MS-specific data (from the *Registre Lorrain des Scléroses en Plaques*, the only regional medical registry in France) to French medico-administrative data, estimated a cost of 15,159€ in 2014 (Bruno et al., 2019). A systematic review estimated a total annual cost per patient in Europe of 40,300€ on average, although differences by geographic areas were observed (Paz-Zulueta et al., 2020). These costs are higher than those estimated in this study (10,318€ and 11,676€ year n-2 and n-1, respectively), which may be explained by our opportunity to perform the analyses by type of MS and to focus on RRMS patients, which disease is less advanced (patients are younger and have a shorter disease history) and less severe (almost two-thirds had an EDSS score <4 vs less than a quarter for SPMS

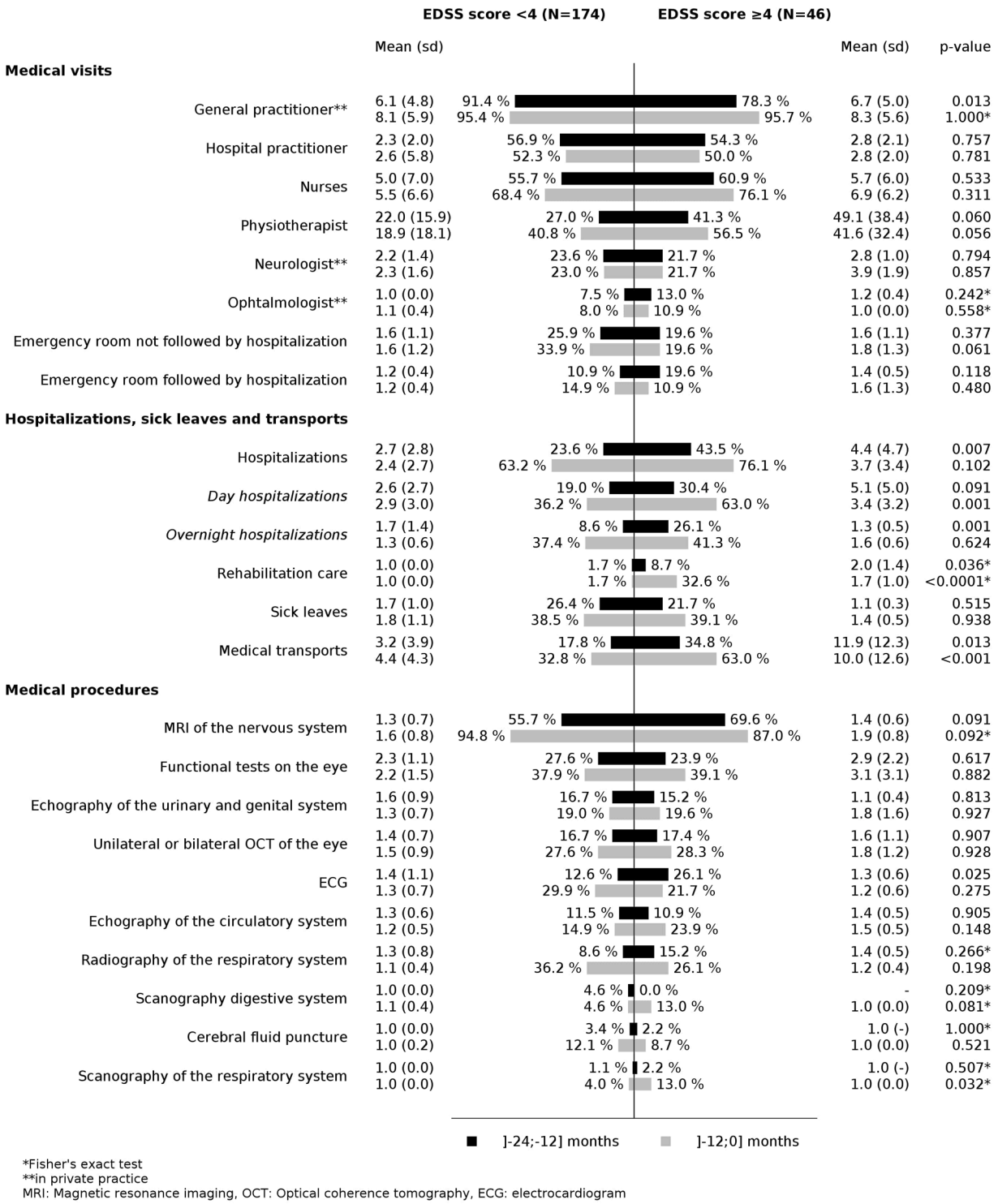

Fig. 4. Outpatient and inpatient management of RRMS patients according to the EDSS score, over year n-2 and n-1: percentage of patients with at least one care and mean number of cares per patient.

patients). However, the breakdown of cost is similar to that described in the literature (Vandhuick et al., 2021, Bruno et al., 2019, Fromont et al., 2014, Lebrun-Frenay et al., 2017, Schauf et al., 2023), i.e. MS-specific DMTs are the main expenditure item, followed by hospitalizations.

This study also confirms that costs increase with the degree of disability, measured by EDSS (19,999€ versus 9813€ the year n-1, for patients with EDSS score <4 and ≥4, respectively). This has also been widely described in other studies performed in France (Bruno et al., 2019, Lebrun-Frenay et al., 2017, Johansson et al., 2012), as well as by systemic reviews carried out in the United States (Schauf et al., 2023) and Europe (Paz-Zulueta et al., 2020). This can be easily explained by a higher need for medical care associated with progressing disability. Indeed, it has been observed in this study that more patients with EDSS score ≥4 were treated with high efficacy treatment, used walking assistance or wheelchair, and were hospitalized. A higher mean number of pain killer dispensations was also recorded.

From year n-2 to n-1, a slight increase in the mean cost was observed and may be the reflect of an increased disease activity, a criterion for

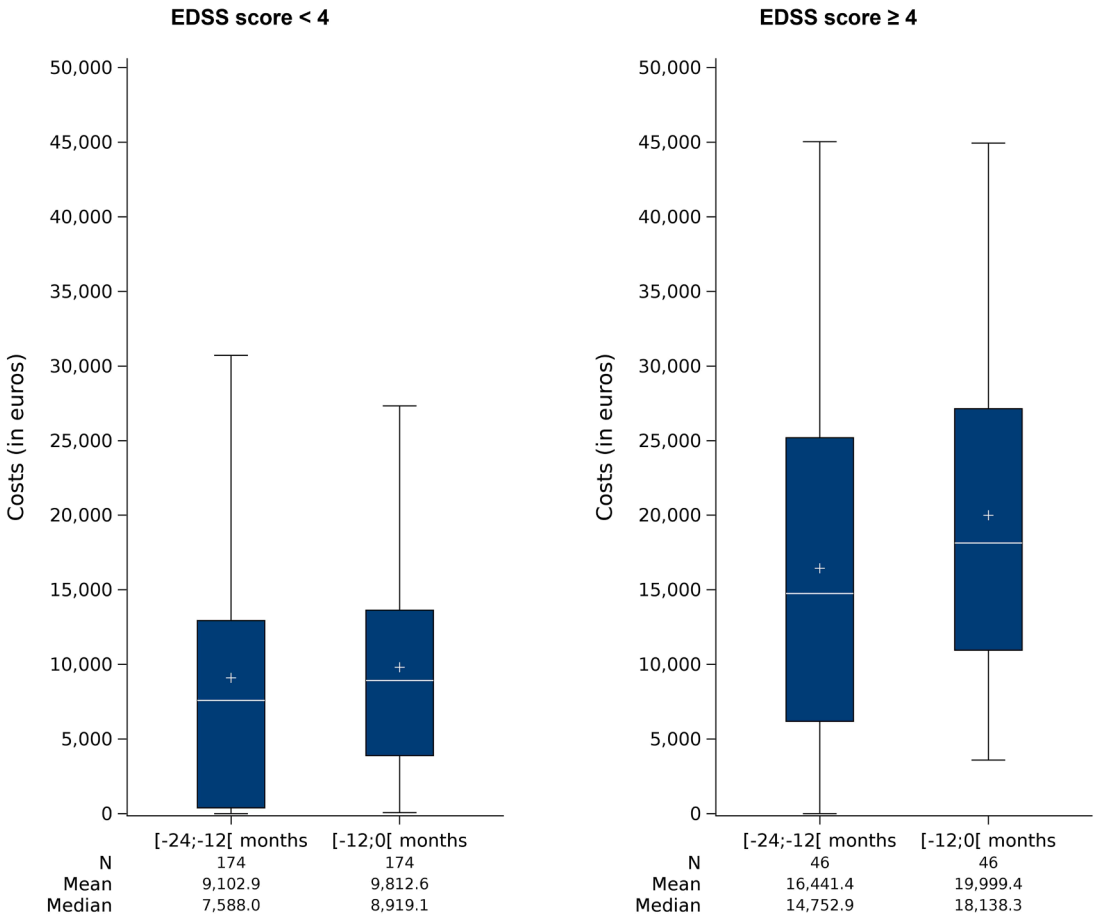

Fig. 5. Boxplots of costs of RRMS patients according to EDSS score, over year n-2 and n-1.

enrolment in the phase IV study. Indeed, two burden of disease studies carried out in France and Canada demonstrated that relapses are associated with increased costs (2305€ per relapse for patients with EDSS ≤6 and CAN$ 10,512 for patients with EDSS score ≤5) (Lebrun-Frenay et al., 2017, Karampampa et al., 2012). Raimundo and al. even showed in a US claims database that costs (excluding DMTs) of patients with two or more relapses per year were almost twice as high as the cost of MS patients with one or no relapse (Raimundo et al., 2013). In this study, the higher number of patients who were hospitalized, benefited from sick leaves and required medical transports the year n-1 is in line with an increased disease activity. However, an MRI of the nervous system was required in the year prior to inclusion, or if not, at inclusion, which explains why over 90 % of patients had an MRI during year n-1.

This study also showed that patients initiating ocrelizumab, as part of the phase IV study, were mostly non-naïve as it was also described by real-word studies in other European countries (Ellwardt et al., 2020, Moccia et al., 2022, Pontieri et al., 2022). A percentage of 38.2 % of naive SPMS patients was not expected given the history of their disease (RRMS that progressed to a more severe progressive form). These patients may have been treated with off-label drugs for progressive MS (mycophenolate mofetil (CellCept), methotrexate (Methotrexate), cyclophosphamide, and azathioprine), which were not studied, or treated >5 years ago (i.e. beyond the study history) (Chedid et al., 2022).

4.3. Strengths and limitations

The SNDS is a comprehensive claims database, including all the reimbursed HRU, which avoids the difficulties associated with data collection, as well as imprecisions and memory biases. It contains some medical data, such as hospital diagnoses, but clinical information as results of laboratory tests or imaging are missing. Hence, there is no data regarding the activity and the severity of the disease. Proxies can be developed for some clinical indicators, but definition and validation of algorithms of identification is a real challenge. Hence, thanks to the linkage performed, the SNDS and the clinical data from the PRO-MSACTIVE study are two complementary data sources. The linkage has enabled us to put into perspective the EDSS score and the type of MS, for which there is no specific ICD-10 code, with the consumption of care and associated costs. As no direct linkage was possible, a deterministic linkage (i.e. combination of variables common to both data sources) was performed, with no possibility of checking if the patients were linked to the good one. However, it was considered unlikely that two patients of the same sex and age would have an infusion on the same day in the same hospital. As 71.4 % matched on these variables, the level of confidence in the linkage is high. Moreover, we can consider that there is no selection bias as almost 80 % of patients were linked and characteristics of linked and unlinked patients were quite similar. Although it constitutes a specific population due to clinical setting (patients with an active RMS) and that results cannot therefore be generalized to the general MS population, exclusion criteria were limited and the phase IV was bordering on a pragmatic clinical trial. Unfortunately, the number of SPMS patients linked was too small to describe HRU and associated costs according to EDSS score. Moreover, the number of RRMS patients with an EDSS score ≥4 was only 46 patients and no adjustment for confounding factors were performed when comparing populations. The results should therefore be interpreted carefully. There is limited economic data available when a treatment change occurs. The data from the PRO-MS study dates back to 2019/2020, and clinical management has evolved since then, particularly with the introduction of new treatments

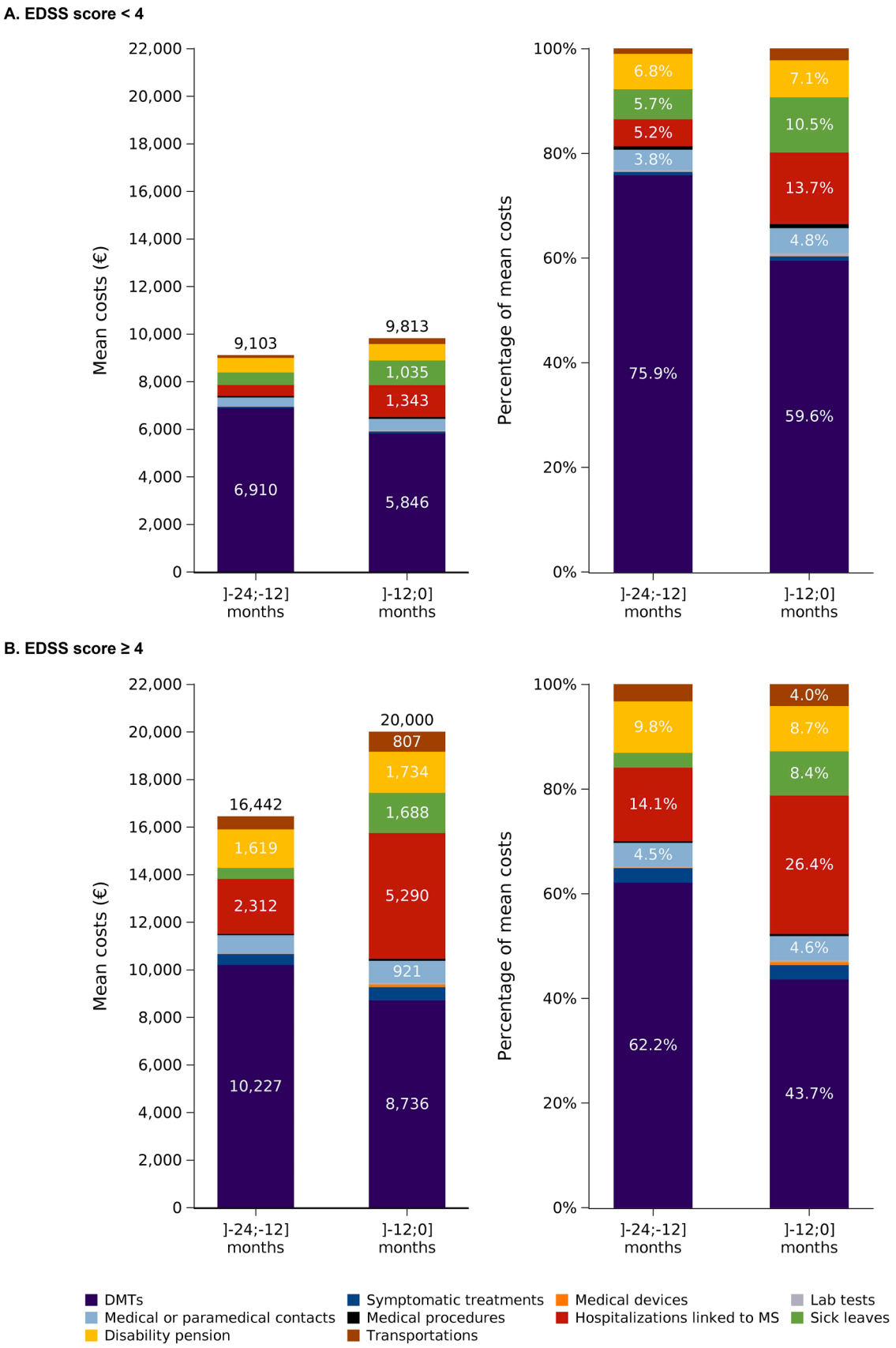

Fig. 6. Costs per health expenditure item for patients with RRMS, according to EDSS score, over year n-2 and n-1.

such as ofatumumab, for which medico-economic analyses would be valuable. Additionally, the spacing of ocrelizumab doses has been implemented recently, leading to a reduction in treatment costs.

5. Conclusion

This burden of disease study is the first to combine clinical data from a phase IV study with claims data from SNDS, enabling to leverage data that are not initially collected in a trial, such as healthcare costs, and to describe these costs according to clinical characteristics from the trial, that are missing in the claims database. It allowed us to estimate the greater burden of RRMS patients with a higher level of disability (EDSS score $\geq$4) and to evaluate the increase in HRU associated with the disease activity the year before enrolling in the phase IV study.

Ethics approval statements

This study was approved by the French Health Data Hub (approval No3471595bis from May 6, 2021) and the French Data Protection Authority (CNIL; approval No 921,221 from September 15, 2021).

Consent to participate

An information note was sent to each patient in the ML40359 PRO-MSACTIVE study.

CRediT authorship contribution statement

Xavier Moisset: Writing – review & editing, Supervision. **Grégoire Mercier:** Writing – review & editing, Supervision. **Manon Belhassen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Floriane Deygas:** Writing – review & editing, Formal analysis. **Alexandre Civet:** Writing – review & editing, Supervision, Methodology. **David Pau:** Writing – review & editing, Supervision, Methodology. **Laure Rolland:** Writing – review & editing, Supervision, Methodology. **Guillaume Bourel:** Writing – review & editing, Supervision, Methodology. **Sophie Larrieu:** Writing – review & editing, Supervision. **Clarisse Marchal:** Writing – original draft, Conceptualization.

Declaration of competing interest

MB, FD and CM are full time employees of PELyon. AC, DP, LR and GB are full time employees of Roche SAS. GM and SL have no conflicts of interest to declare. XM has received financial support from Allergan-Abbvie, Aptis Pharma, Biogen, BMS, Grünenthal, Lilly, Lundbeck, Teva, Merck-Serono, Novartis, Orion, Pfizer, Roche, and Sanofi-Genzyme and non-financial support from SOS Oxygène not related to the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106305.

Data availability

The datasets presented in this article are not readily available because, due to NHS and SNDS rules, no data sharing is possible as access to data is restricted to habilitated and qualified researchers (Floriane Deygas is habilitated and qualified).

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